REMARKS/ARGUMENTS

Claim Status.

Claims 1, 2, 4, 6, 28 and 30 are currently pending and claims 1, 4, 28 and 30 will be pending upon entry of the present amendment. Claim 1 has been amended to more particularly point out and distinctly claim that which Applicants consider to be the invention. This amendment is discussed below and is supported in the specification as filed, thus, no new matter has been introduced. Claims 2 and 6 have been cancelled.

Requirements

In paragraph three, page 2 of the Office Action, it is stated that reference within a specification to a citation does not count toward official consideration unless the document is cited in an official PTO form. The Examiner states that only documents cited in a PTO-892 have been considered. However, it is noted that a proper Information Disclosure Statement and Form 1449 were submitted to the Office and signed and returned as part of Paper 7 mailed May 5, 2001, thus the documents cited therein are unquestionably of record at this time. In addition, a supplemental IDS with Form 1449 was properly submitted on April 10, 2002 but has not yet been processed by the Examiner.

In paragraph 4, page 3 of the Office Action the Examiner has required that a supplemental oath or declaration be submitted as the pending claims allegedly no longer substantially embrace the invention as set forth in the original claims. Representative for the applicants protests this requirement. The originally filed claims and those currently pending are fully commensurate in scope. In fact, the current claims relate to a narrowed set of molecules encompassed by the originally pending claims. Thus it is unclear why this requirement has been put forth and withdrawal or clarification of this requirement is earnestly requested.

Objections to the Specification

In paragraph 5, page 3, the Examiner objects to the specification as having improperly used incorporations by reference. However, there is no specific example of how these references are needed for the claimed invention. In other words, the incorporations are not cited in any of the subsequent rejections and there isn't any issue or harm. Thus it is unclear what the Examiner is now demanding and clarification of this objection, or it's withdrawal, is requested.

In paragraph 6, page 4, a new title was required and has been provided herein.

Objections to the Claims

Claims 2 and 6 have been objected to under 37 CFR 1.75(c). More specifically, the Office Action states that claim 2 is improper for failing to further limit the subject matter of a previous claim from which it depends and claim 6 is improper as being dependent from cancelled claim 5. Applicant's have cancelled these claims and this objection is now overcome.

Rejection under Section 112, first paragraph.

Claims 1, 2, 4, 28 and 30 are rejected as not enabled for several reasons.

Firstly, in paragraph 11, pages 5-6, the Office Action states that the wording of the independent claim is internally contradictory as to whether the pharmacologically active unit is Fc or IL-1ra. In response, claim 1 has been amended to clarify that the pharmacologically active unit is the IL-1ra and that this unit is fused to an Fc domain. This part of the rejection is overcome by this amendment.

Secondly, in paragraphs 12-13, pages 6-7 of the Office Action it is alleged that the specification does not provide a working example and there are no 'starting materials' for the invention, therefore it is not enabled. In support of this position, *Genentech v. Novo Nordisk A/S* is cited. It is respectfully submitted that the facts and decision in *Genentech v. Novo Nordisk A/S* do not apply to the pending application and there are in fact sufficient starting material to enable the claimed invention. In the *Genentech* decision, the Federal Circuit explained that there must be some disclosure of starting material in order for the specification to teach how to use an invention. However, in that specific situation, Genentech had claimed a cleavable protein but did not describe any proteases that could be used in their system. Genentech did provide a description of trypsin, but it was held by the Court that it is well known that trypsin digests proteins too frequently and is useful only for general digestion and not selective cleavage as claimed. Indeed, the Court in *Genentech* goes on to state that as of the filing date of the patent at issue, 'no one had been able to produce *any* human protein via cleavable fusion expression' [emphasis in original], *Genentech v. Novo Nordisk A/S* 42 USPQ2d at 1006, (Fed Circ. 1997). Thus, without providing any examples, even prophetic, of a workable enzyme that could be used for selective cleavage, the Court found that the patent lacked enablement. In complete contrast, the present specification provides a detailed teaching of how to use the claimed method of refolding a protein using a copper halide, and even provides an explicit working example. Even though this working example is with a different protein than what is claimed, the description of successful application of the method combined with teaching of the claimed protein that is the pharmacologically active unit provides sufficient starting material to enable the claimed invention. The method was demonstrated to work, and the protein that is used in the claimed method is provided in adequate detail to enable the invention. Accordingly, it is respectfully submitted that *Genentech* does not

apply to the current factual situation, that there is indeed sufficient starting material to enable the invention, and withdrawal of this part of the rejection is requested.

And Finally, in paragraph 14, page 7 of the Office action, because there is no upper limit to the concentration of copper halide it is alleged that the claims could encompass glacial solutions. This is not correct. The use of glacial solutions would almost certainly result in non-active non-pharmacological compounds that are outside the claims which recite a pharmacological active compound. The fact that there is no cited upper limit is not detrimental to the determination of the useful ranges of copper halides because it would be routine experimentation to find these limits given the teachings of the disclosure. Indeed, the Examiner notes in this response in a different section (specifically page 27, line 5 of the Office Action) that the variation of concentrations is merely routine experimentation. Thus, having found a minimum concentration that is effective for refolding of proteins, it is submitted that it is merely routine experimentation to determine the upper limit of the useable concentration, and in combination with the pharmacological activity limitation, it is unnecessary to provide an upper limit to the copper halides.

It is respectfully submitted that the above-made amendments and arguments overcome this rejection and withdrawal is requested.

Rejection under Section 112, second paragraph

Claims 1, 2, and 6 are rejected as indefinite. As discussed above, and in response to the Examiner's helpful suggestion in this section, claim 1 has been amended so that it recites IL-1ra as the pharmacological agent and Fc as the fusion partner. In addition, claims 2 and 6 have been cancelled, thus it is submitted that the pending claims are definite and withdrawal of this rejection is respectfully requested.

Rejection under Section 103.

Claims 1, 4 and 6 are rejected as unpatentable over Bendele et al. (WO 98/24477 A1) in view of Hannum et al. (US Patent 5,075,222) and Halenbeck et al. (WO 88/08003 A1). Bendele teaches IL-1ra and that it can be produced via recombinant means. Hannum teaches IL-1ra alpha and beta and cloning the sequences into *E. coli.* Neither of these references teach refolding of Fc proteins using copper halides. Halenbeck discloses the oxidation of colony stimulating factor-1 (CSF-1) produced in *E. coli* using cupric chloride on page 43. The Office Action alleges that since the CSF-1 of Halenbeck is treated with cupric chloride (page 43) and that the concentration of cupric chloride, while low at 50 micromolar, it is within the realm of routine optimization. Thus it is alleged that one would have been motivated to use cupric chloride to refold IL-1ra fused to an Fc domain (paragraph 27, page 11 of the pending Office Action).

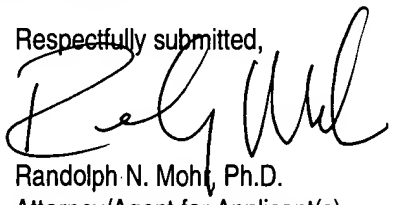
Applicant's representative respectfully disagrees for the following reasons. Halenbeck teaches the use of low concentrations of cupric chloride for oxidation of an already refolded protein. The Examiner's attention is directed to page 42, line 34 to page 43, line 6 of Halenbeck where it is taught that CSF-1 is refolded in the presence of glutathione among other chemicals, and then later, the already refolded protein is treated with cupric chloride to effect oxidation (page 43, lines 21 to 28). This is different than the process described and claimed by the present inventors where much higher concentrations of a copper halide are used to refold the protein of interest where the copper is the primary driver of proper disulfide formation and refolding. Thus it cannot be held that variation of the teachings of Halenbeck that may encompass the presently claimed invention would be routine because the purpose of the use in Halenbeck was different. It is not even clear if the use of at least 10 mM copper halide would be useful in the Halenbeck example for oxidation as opposed to refolding as presently taught and claimed. Accordingly, Halenbeck does not teach any treatments of IL-1ra molecules, let alone treating IL-1ra molecules fused to a second protein sequence such as an Fc domain with any chemicals for the purpose of refolding. This combined with the acknowledged fact that the Bendele and Hannum references also do not teach copper mediated refolding of IL-1ra fusion molecules, there is no teaching or suggestion in the cited references to perform the described and claimed methods.

Thus, in light of the amended claims and the arguments presented above, it is respectfully submitted that obviousness in light of the cited references does not apply and withdrawal of this rejection is requested.

Conclusion.

In light of the foregoing amendments and remarks, the Applicants respectfully request entry of all amendments, withdrawal of all rejections and objections, and allowance of all claims.

Respectfully submitted,



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